REMARKS

I. Non-Statutory Double Patenting Rejection

Applicants traverse this rejection by filing a terminal disclaimer disclaiming any term after the expiration of U.S. Patent No. 5,750,110.

II. Enablement Rejection

A. Introduction

The Examiner has rejected pending claims 19-20 and 23-24 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in a manner to enable one of ordinary skill in the art to make and/or use the invention claimed in the application. More specifically, the Examiner argues that the specification sets forth "no convincing evidence of vaccine efficacy with respect to HIV." (Office Action of Sept. 14, 1999 at 4.)

Applicants' invention is a vaccine comprising: HIV antigen, QS-21, and 3-De-O-acylated monophosphoryl lipid A (3D-MPL). Applicants have submitted uncontroverted evidence that their invention effectively protects rhesus macaques from SHIV challenge. Applicants have also submitted evidence that efficacy of the SHIV/macaque model reasonably correlates with the human/HIV model and, therefore, Applicants meet the requirements of section 112, first paragraph.

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B. The Examiner's General Arguments Against HIV Therapies are Not Specific to the Applicants' Invention and are Insufficient to Maintain the Rejection

The Examiner's first argument is merely a general list of obstacles to HIV therapy. The Examiner does not respond to Applicants' evidence from their Appeal Brief pointing out that these obstacles are not unique to HIV. As pointed out in the Applicants' Appeal Brief, the PTO has already allowed claims[1] directed to vaccines for diseases that have several of the obstacles identified by the Examiner (Appeal Brief at p. 13.) For this reason alone, the Examiner's arguments cannot be supported. Moreover, despite the Examiner's arguments, the PTO has allowed claims directed to HIV therapies in other patents.

For example, in U.S. Patent No. 5,789,388, the PTO allowed a claim to a vaccine for protecting a host comprising a live pseudorabies virus vector wherein that vector harbors a gene encoding an antigen of a virus. The patent teaches, and the claims recite, that that virus may include HIV. (Col. 8, lines 34-41, 47-51.) In another example, the PTO issued U.S. Patent No. 5,512,281 which includes claims directed to prophylactic methods of treating pregnant women carrying an HIV-1 infection to prevent infection of the fetus. (Col. 14, lines 32-40.) Thus, as the PTO continues to issue patents for treatments directed to HIV therapies, the Examiner cannot maintain a

[1] *See* U.S. Patent No. 5,750,110.

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rejection based on general obstacles to HIV therapies. Accordingly, the Examiner's general arguments cannot be maintained.

The key question here is not whether there are general obstacles to development of anti-HIV therapies such as vaccines. Rather, the important issue centers around the Applicants' invention of specific vaccines and the body of evidence they submitted demonstrating the efficacy of that invention. That evidence demonstrates Applicants' compliance with the requirements of section 112, first paragraph.

C. The Applicants' Animal Model is Accepted in the Art

1. The PTO has issued a Patent Directed to the SHIV Model

After a discussion of generic rationales for maintaining the rejection, the Examiner's second argument attempts to refute the Applicants' data. That data, submitted earlier in prosecution, shows the considerable success Applicants have had with the SHIV/macaque model. Indeed, 10 of the 12 vaccinated macaques challenged with SHIV showed no signs of infection at each testing interval after challenge. Further, Applicants submitted evidence showing the superiority of the SHIV/macaque model to any other model and that it reasonably correlates with human HIV infection. (Appeal Brief at pp. 19-20.) The Applicants' arguments are further supported by a recently issued patent.

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In U.S. Patent No. 5,849,994 ("the '994 patent"), an animal model of HIV-1 induced disease is described and claimed. The specification teaches that prior to the invention by the patentees, the SHIV model suffered from a drawback because macaques did not get disease despite "prolonged persistent infection." (Col. 1, line 63.) The patentees further note:

> The instant invention solves this problem by providing pathogenic SHIV which causes AIDS like syndromes in macaques, methods for the generation of pathogenic SHIV, and also providing methods and compositions for the production of an animal model for HIV-1 induced disease.

(Col. 1, line 65-col. 2, line 2.) Indeed, in the Voss declaration of April 1998, Applicants stated that the SHIV/macaque model was an art-recognized model because, among other reasons, the macaque is capable of progressing to AIDS once infected with SHIV. (Voss Dec. Apr. 1998, Par. 10.) The '994 patent also teaches that the SHIV model provides an animal model for studying HIV infection in humans.

> The instant invention provides pathogenic virus for creating animal models for HIV-1 infection.

Col. 4, lines 13-14. Thus, the Applicants' model is an art-recognized model and the Examiner's arguments cannot be sustained.

2. The Applicants' Model is Distinct and Superior to the Models Criticized in the Art Cited by the Examiner

The Examiner also relies on articles by Haynes, Cohen, and Butini for the proposition that there are no art-recognized animal models of HIV infection. This

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reliance is misplaced. For instance, although Haynes states that "current" animal models do not exactly mirror HIV infection in humans, no discussion is made of the use of Applicants' SHIV/macaque model. A closer inspection of Haynes also reveals that for the proposition that current animal models are inadequate, Haynes cites his 1993 article in *Science*–two years before the filing date of the '994 patent. The latter-published Haynes reference merely criticizes the chimpanzee animal model, a model not used by the Applicants. It also criticizes models that "lack immune responses analogous to human anti-HIV T and B-cell responses." (Haynes at p. 40.) According to Dr. Voss, however, in the SHIV/macaque model, "[i]nfected animals mount a vigorous immune response similar to those observed in infected humans, including CD8+CTL." (Voss Decl., April 1998, Par. 10.) Thus, the Haynes criticism of animal models does not apply to the SHIV/macaque model used by the Applicants. The Examiner cannot reasonably rely on a statement based on a 1993 scientific article for the proposition that today, seven years later, the art does not recognize an animal model in the face of evidence submitted by the Applicants and the teachings of the '994 patent.

The other articles cited by the Examiner for the general proposition that successful therapies against HIV face obstacles are also considerably outdated. The '994 patent, directed to the successful SHIV animal model, was filed in 1995, over one year after the publication of Butini and two years after the publication of Cohen.

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The Examiner cites *In re Hartop*, 135 USPQ 412, 426 (CCPA 1962) for the proposition that correlations between results observed and probable results in humans are an important concept in the "standard experimental model." The Court went on to rule, however, that the applicants had met the statutory utility requirement despite the fact that "no clinical evidence" was submitted showing the safety of the claimed solutions. *Id.* Further, as pointed out already by the Applicants, "[e]vidence does not have to be in the form of data from an art-recognized model for the particular disease or disease condition to which the asserted utility relates." (MPEP §2107.02.) Indeed, the MPEP further requires that "Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application." *Id.* The Examiner also suggests, based on quotations from Haynes that only human clinical trials will show the efficacy of a vaccine. The PTO specifically instructs, however, that applicants cannot be forced to submit human clinical data:

> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials.

Id. All that is required is that "one of ordinary skill in the art would accept the animal tests as being reasonably predictive of utility in humans." *Id.* (Emphasis in original.)

The Applicants have submitted two declarations from Dr. Voss, one of at least ordinary skill in the art, and test data proving that the invention claimed effectively

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protected 10 of 12 rhesus macaque from challenge with SHIV. That evidence along with other art, including the '994 patent, demonstrate the reasonable correlation between the Applicants' data and efficacy in humans. Applicants have gone even further by showing that the SHIV/macaque is an art-recognized model, and Applicants easily meet the requirements of § 112, first paragraph. Indeed, even in this very office action, the Examiner seems to concur by arguing as a basis for the obviousness-type double patenting rejection that:

> One of ordinary skill in the art would have been motivated by the long felt need for a vaccine and would have had a reasonable expectation of success since the claimed invention of U.S. Patent No. 5,750,110 were broadly claimed and used for many different antigens of widely varying sources.

(Office Action, p.3 (emphasis added).) As the Applicants have met the statutory requirements under section 112, this case is in condition for immediate allowance.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the timely allowance of the pending claims.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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